

Swiss clinical practice guidelines for skin cancer in organ transplant recipients

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Summary

Patients with a solid organ transplant have increased in numbers and in individual survival in Switzerland over the last decades. As a consequence of long-term immunosuppression, skin cancer in solid organ recipients (SOTRs) has been recognized as an important problem. Screening and education of potential SOTRs about prevention of sun damage and early recognition of skin cancer are important before transplantation. Once transplanted, SOTRs should be seen by a dermatologist yearly for repeat education as well as early diagnosis, prevention and treatment of skin cancer. Squamous cell carcinoma of the skin (SCC) is the most frequent cancer in the setting of long-term immunosuppression. Sun protection by behaviour, clothing and daily sun screen application is the most effective prevention. Cumula-

tive sun damage results in field cancerisation with numerous in-situ SCC such as actinic keratosis and Bowen's disease which should be treated proactively. Invasive SCC is cured by complete surgical excision. Early removal is the best precaution against potential metastases of SCC. Reduction of immunosuppression and switch to mTOR inhibitors and potentially, mycophenolate, may reduce the incidence of further SCC. Chemoprevention with the retinoid acitretin reduces the recurrence rate of SCC. The dermatological follow-up of SOTRs should be integrated into the comprehensive post-transplant care.

Key words: organ transplant; squamous cell carcinoma of the skin; prevention; sun protection; immunosuppression; chemoprevention

Introduction

Over the last three decades, improved surgical techniques and advances in immunosuppressive medication have allowed more and more patients to benefit from solid organ transplantation. Worldwide the number of solid organ transplantations performed and graft survival have increased impressively. Graft rejection is suppressed by combined immunosuppression, which in turn increases rates of infection and cancer as adverse events. Cutaneous infections (e.g., human papilloma virus (HPV)) and neoplasms (e.g., non melanoma skin cancer (NMSC) with squamous cell carcinoma of the skin (SCC) in particular) affect the majority of solid organ transplant recipients (SOTR) during the course of long-term immunosuppression [1].

The increased numbers of transplantations associated with the improved patient and graft survival greatly increase the numbers of SOTR in need of dermatological care. In an attempt to enhance the awareness among dermatologists and other physicians regarding the importance of careful dermatological monitoring of SOTR for early diagnosis and prompt treatment, several collaborative groups of dermatologists have recently emerged: The US-led International Transplant – Skin Cancer Collaborative (ITSCC), the European Skin Care in Organ Transplant Recipients Europe (SCOPE) Network and, in Switzerland, the Swiss Society for Dermatology and Venerology (SGDV) working group for organ transplantation.

For the *SGDV working group for organ transplant recipients, ** SGT Swiss Society of Transplantation, *** SGN Swiss Society of Nephrology

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Joint American and European guidelines for the prevention and treatment of skin cancers in SOTR have recently been published [2]. They are, however, somewhat general in nature due to the lack of large scale long-term studies addressing the care of SCC in SOTR. In order to assist Swiss physicians in the management of SOTR, the SGDV working group for organ transplantation has, in collaboration with the Swiss Society

of Nephrology and the Swiss Society of Transplantation, put together the present clinical guidelines for the management of skin cancer in SOTR. We based these recommendations on the best available evidence and on collective clinical experience. Our recommendations are graded in accordance with the Oxford Centre for Evidence-Based Medicine [3].

Pretransplantation screening

A dermatological consultation is recommended before transplantation to examine and/or to treat current skin disease, in particular skin cancer, to assess the risk of skin tumours following transplantation and to instruct the patient in prevention and early recognition of skin disease (recommendation level D) (table 1) [4]. History-taking should cover extent of lifetime UV exposure, frequency of sunburns, patient and family history of skin cancer as well as past and present HPV-associated verrucae, actinic keratosis (AK), Bowen's disease (BD) and invasive skin cancer, in particular

SCC, basal cell carcinoma (BCC), melanoma, Kaposi's sarcoma (KS) and Merkel cell carcinoma (MCC). The history should also include previous long-term immunosuppression such as the use of azathioprine or calcineurin inhibitors for vasculitis, glomerulonephritis or a previous solid organ transplant. Other factors causing immunosuppression such as HIV status should be noted. A positive history for SCC and BCC is associated with increased risk for these tumours following transplantation (recommendation D). Risk factors for NMSC in SOTR are given in table 1. A total body skin examination covering the oral and anogenital region should be performed. Counselling should explain the importance of UV in skin carcinogenesis, teach sun avoidance by behaviour, clothing and daily sun screen application. Tanning bed use should be discouraged. Early recognition of skin cancer should be taught. Phototherapy should be avoided in potential organ transplant recipients (e.g., nephrogenic pruritus) to limit further UV damage and skin carcinogenesis (recommendation D).

Warts, AK, and BD should be treated before transplantation. AK should be understood as a symptom of photodamaged skin with field cancerisation and prompt a higher frequency of dermatological consultations. Invasive skin cancer should be removed surgically. High-risk squamous cell carcinoma should be discussed with the transplant physician and may require an observation period before transplantation. Metastatic skin cancer is generally an exclusion criterion for transplantation. A history of melanoma should be carefully evaluated, in particular if the primary melanoma measured >1 mm Breslow tumour thickness and/or diagnosis was made less than 5 years priorly (recommendation D) [5, 6]. Particular care is mandated in the evaluation and management of candidates for a second or subsequent solid organ transplant.

Table 1

Pre-transplantation screening recommendations.

History including skin cancer risk factors	Light skin type (Fitzpatrick I/II)
	High UV lifetime exposure with actinic damage
	Personal history of AK, BD, SCC, BCC, other skin cancer
	Family history for skin cancer
	Previous exposition to immunosuppressive drugs (type and length)
Examination	Total body skin examination including oral and genitoanal region
Treatment	Treat present AK, BD, verrucae
	Remove invasive skin cancer
Education	Sun avoidance by behaviour, clothing, daily sun screen application
	Avoid in-door tanning beds
	Self-skin examination monthly, dermatological examination yearly
	Present to dermatologist for growth >4 weeks, wound non-healing >4 weeks
Dermatological recommendation to transplant physician	Avoid phototherapy
	Discuss patient eligibility for transplantation in case of skin cancer
	Initiate retinoid chemoprophylaxis in case of skin cancer
	Consider early switch to mTOR inhibitors in case of skin cancer

Patient education: Sun protection and self-skin examination

SCC is the most common cancer in the post-transplant setting [7]. After immunosuppression, UV is the main factor in cutaneous carcinogenesis [8]. Immediate post transplant advice is generally not associated with sun-protection behaviour, such as use of sun screen, probably because of stress in the peritransplant period [9]. Long-term sun protection behaviour in SOTR needs to be improved [10]. Therefore, all SOTR should receive education about their increased risk of skin cancer, sun protection and self-skin examination before transplantation and, thereafter, on at least a yearly basis by a dermatologist (recommendation D).

Education should cover the clinical appearance of common benign, premalignant and malignant skin lesions. UV protection is based on the three pillars of avoidance, clothing and sun screen. Avoidance of sun exposure, particularly between 11am and 3pm, should be recommended. Patients should wear a hat with a wide brim, sunglasses, long sleeves and trousers whenever possible. The regular use of high sun protection factor sunscreens significantly reduces the frequency of precancerous and cancerous skin lesions [11]. Sunscreens with UVA protection (e.g., Australian norm) and a high sun protection factor for UVB (e.g., 50+) are thus

recommended for the sunexposed skin of the face, ears, neck and back of the hands every day, rain or shine. Tanning bed use is also to be discouraged in the post-transplant period (recommendation D).

Patients should be encouraged to perform self skin examination monthly looking for skin cancer and precursors. In particular they should look for any new or changing growths including pink patches or spots, scaly growths, bleeding spots, or changing moles. In addition, for high risk patients (i.e., history of high risk squamous cell carcinoma, melanoma or metastatic disease) a self examination of the lymph nodes every month is recommended [8]. A growth occurring for >4 weeks or a wound without healing >4 weeks merit dermatological evaluation (recommendation D).

Patient education addressing sun protection and self-skin examination should be repeated at the recommended yearly dermatological examination. Written information should be provided to reinforce the oral message delivered by the dermatologist (recommendation D) [12]. Adequate information material can be provided by the authors of the current guidelines on request (http://www.derma.ch/derma/resources/Members_AG_OTR_081112.pdf).

Standard management post transplantation

Organ transplant recipients (as well as other patients on long-term immunosuppression) should be seen by a dermatologist on a yearly basis [4]. The consultation should cover history of new skin lesions, sun protection knowledge and behaviour and self-skin examination habits. Written information material on this educational content should be provided. A full skin examination should be performed with inspection of the palms and soles, oral cavity, genitalia and scalp and – for patients with a history of skin cancer – palpation of the lymph nodes. Lymph node palpation should include the parotid gland, a frequent location for metastatic SCC originating in the facial region (recommendation D).

Potentially due to reduced inflammatory peritumoral infiltrate due to the immunosuppressive regimen [13], invasive SCC may appear clinically less conspicuous than in the general population and is therefore frequently underestimated. Invasive SCC and lentigo maligna may progress rapidly in SOTR [14]. The patient should be advised to report immediately if tumours arise, and the physician must expect SCC and BCC also more often on less common sites like trunk, lower extremities and ears [15], as well as doubling of size within a few weeks [1]. Many other skin diseases such as infec-

tions or drug reactions manifest in a clinically atypical presentation in SOTR [16, 17]. Biopsy should thus be liberally performed to validate the clinical diagnosis, direct appropriate therapy and to remove skin cancer at an early stage. Viral warts can be recalcitrant and may need to be treated more aggressively [18]. Minor injuries like cut wounds and fissures can lead to unusual infections and should not come in direct contact to food, plants, animals or earth (recommendation D).

In newly transplanted or younger recipients, the focus of the yearly consultation should be on education for prevention. In patients with antecedents of skin cancer, dermatological consultations should occur more frequently [8] with a focus on early recognition of skin cancer and treatment of field cancerisation. Unpublished data suggest cost-savings in the dermatological cost of care if an occurrence of invasive SCC can be avoided by prevention and early intervention in SOTRs (Rüegg et al. in preparation). Currently, there are no published data to assess the cost-effectiveness of the recommended consultation intervals. Table 2 summarises our recommendations for dermatological consultation (recommendation D).

Management of skin cancer

a) In-situ SCC (actinic keratosis and Bowen's disease)

Early recognition and early therapy of these lesions is recommended to prevent the development of invasive tumours. Typical AK lesions characterised by hyperkeratosis and macular erythema may be treated without histological confirmation. However, the threshold for biopsy should be low and any questionable, indurated, progressive or refractory lesion should be biopsied (recommendation D).

Treatment modalities recommended are summarised in table 3. Currently, data clearly distinguishing one of these modalities as best are lacking. All treatment choices show clinical efficacy. Generally, however, longer treatment periods,

more frequent applications and occlusive dressings may be required for success compared to the general population. Because of concerns about additional DNA damage and reduced lag time until radiation-induced cancer induction, radiotherapy should not be performed for in-situ skin cancer in SOTR and avoided if possible in invasive SCC.

Field cancerisation refers to a concept of large areas of sun-damaged skin giving rise to in-situ and invasive skin cancer repeatedly [19–21]. Early treatment of field cancerisation may slow subsequent tumour development. Frequently used modalities for the treatment of field cancerisation are 5-FU topically, imiquimod, and photodynamic therapy (cf. table 3).

Table 2

Recommended dermatological consultations in SOTR.

In all situations: Exchange information and discuss management with transplant team and primary physician in charge of the transplant recipient.

Situation	Frequency	Typical contents
Pre-transplant	Once	History Education full skin examination recommendation to transplant physician
Post-transplant	Yearly	Education full skin examination
In-situ SCC (actinic keratosis, Bowen's disease)	Every 6 months	Education full skin examination Topical treatment of field cancerisation
Early cutaneous carcinogenesis (1 to 4 NMSC/year)	Every 4–6 months	Education full skin examination Topical treatment of field cancerisation Surgical removal of invasive SCC Consider systemic retinoids Notify transplant physician
Moderate cutaneous carcinogenesis (5–10 NMSC/year)	Every 2–4 months	Education full skin examination Topical treatment of field cancerisation Surgical removal of invasive SCC Initiate systemic retinoids Contact transplant physician Recommend reduced immunosuppression Consider switch to mTOR inhibitors
Severe cutaneous carcinogenesis (>10 NMSC/year)	Every 1–3 months	Education full skin examination Topical treatment of field cancerisation Surgical removal of invasive SCC Initiate systemic retinoids Contact transplant physician Recommend reduced immunosuppression Consider switch to mTOR inhibitors

b) Invasive SCC

Excision is the therapy recommended for invasive SCC. This also extends to keratoacanthoma, which histologically can not be clearly distinguished from highly differentiated SCC. Keratoacanthoma in SOTR should be considered as SCC and therefore treated as such by complete excision. Complete surgical removal at an early stage is the best prevention of later metastasis, a significant problem in SOTR. Early biopsy in suspicious lesions is strongly recommended (recommendation D). Standard surgery with margin control should respect margins of 4 to 6 mm beyond any surrounding erythema [65]. Mohs micrographic surgery is warranted in anatomic sites where tissue conservation is desired [55, 64]. Extensive local disease, spread to lymph nodes or to distant organs will require individualised and collaborative treatment. Once SCC has occurred, SOTR should be seen at closer intervals, as indicated in table 2. Table 3 lists recommendations for SCC management.

c) Basal cell carcinoma

Treatment of basal cell carcinoma in SOTR should be performed according to recommendations for the general population, as recently reviewed elsewhere [22]. Because of concerns about additional DNA damage and reduced lag time until radiation-induced cancer induction, radiotherapy is not recommended for basal cell carcinoma in SOTR (recommendation D).

d) Melanoma

The incidence of melanoma in SOTR is subject to debate. Compared to the general population, some authors deny any increase [23] whereas others report an up to 8-fold increase [24]. A recent study [25] found a similar outcome of melanoma in SOTR as compared to prognostically matched non-immunosuppressed patients. A larger case series of melanoma in SOTR came to a similar conclusion (for melanoma <2 mm Bres-

low thickness), but it found that the outcome for melanoma >2 mm Breslow is worse in SOTR than in the general population [26]. Currently, limited by the relatively small numbers reported, we recommend that melanoma in SOTR should be treated according to generally applicable guidelines (recommendation C) [27, 28]. The benefit of reducing or switching immunosuppression in metastatic melanoma remains unclear and should be weighed on an individual basis [29].

e) Kaposi sarcoma

The iatrogenic variant of Kaposi sarcoma

(KS) is 400- to 500-fold increased in SOTR [30] and occurs in 0.4% of US and European SOTR [31–33], and in up to 5.3% of SOTR in Saudi Arabia [34]. KS prevalence after organ transplantation varies greatly depending on the prevalence of HHV8 infection in the general population. Most cases of post-transplant KS develop as a result of viral reactivation [35]. Ethnic background should thus be considered in the differential diagnosis of KS. Although HHV8 viral load in peripheral blood mononuclear cells of KS individuals correlates with tumour burden, due to low interval variations this test cannot be used in clinical

Table 3

Recommendations for the management of primary SCC in SOTR.

Situation	Action	Comment
Treat in-situ SCC (actinic keratosis, Bowen's disease) and field cancerisation	Cryotherapy [51]	
	Topical 5-fluorouracil [52]	
	Topical imiquimod [53]	
	Topical photodynamic therapy [54]	
	Curettage [55]	
	Electrodesiccation [55]	
	Avoid radiotherapy	Additional DNA damage, subdued inflammatory response
Document invasive SCC [2]	Biopsy to recognise invasive SCC	Palpable, refractory, enlarging lesions
	Lesion history	duration, growth rate, previous treatment, associated pain
	Site and size of lesion	
	Histology	subtype, differentiation, Breslow thickness, perineural or perivascular involvement, ulceration
	Cutaneous satellite lesions	
	Status of draining lymph nodes	Examine clinically
	Full skin examination	anogenital and mucosal regions included
Recognize less aggressive SCC	Tumour size	<0.6 cm mask area of the face*, genitalia, hands, feet; <1.0 cm cheeks, forehead, neck, scalp; <2.0 cm: trunk, extremities [2, 56]
	Slow growth	
	Lack of ulceration	
	Well-defined clinical margins	
	Lack of satellite lesions	
	Histology	in situ, keratoacanthoma type, well-differentiated, limited to papillary dermis, absence of neurotropism or of perivascular invasion
Recognize aggressive SCC at risk for invasive growth, recurrence or metastasis	Multiple SCC	[2, 57–61]
	Tumour size	>0.6 cm mask area of the face *, genitalia, hands, feet; >1.0 cm: cheeks, forehead, neck, scalp; >2.0 cm: trunk, extremities
	Indistinct clinical borders	
	Rapid growth	
	Ulceration	
	Location on the mask areas of the face, scalp, genitalia, digits and within an anatomic fusion plane	
	Occurrence in a scar, in an area of chronic inflammation or in the field of prior radiotherapy	
	Recurrence after previous treatment	
	Presence of satellite lesion	
	Histology	deep extension of tumour into the subcutaneous fat, perineural invasion, perivascular or intravascular invasion, poor differentiation

* mask area comprises central face, eyelids, eyebrows, periorbital, nose, lips, chin, mandible, preauricular and postauricular areas, temple and ear

practice to monitor KS patients nor to predict the occurrence of KS in transplant recipients [35]. Because of its variable clinical appearance, diagnosis of KS should be sought early by biopsy [36]. In case of KS, the whole skin including the mucosae and in particular the palate should be examined for the presence of further KS lesions. Multiple lesions indicate a higher likelihood of visceral involvement [36]. A diagnosis of KS should be discussed with the multidisciplinary transplant team to determine the work-up for potential visceral involvement.

Reduction of immunosuppression generally leads to resolution of iatrogenic (drug-associated) KS [37–43]. Recently, maintenance of immunosuppression with a switch from calcineurin inhibitors to mTOR inhibitors has proven successful in renal transplant recipients with resolution or stabilisation of KS disease. First-line recommendation is, therefore, notification of the transplant team with the recommendation of a switch from calcineurin inhibitors to mTOR inhibitors,

if this can be performed based on all the variables (e.g., presence or not of significant proteinuria) (recommendation C). This switch in immunosuppression to mTOR inhibitors has mostly been documented in renal transplant recipients and – lacking published data – may not apply to the same extent to other solid organ transplant recipients. Second-line recommendation to the transplant physician is a reduction in immunosuppression (recommendation D). Further treatment modalities are numerous and have been reviewed extensively elsewhere [36].

f) Rare types of skin cancers

Merkel cell carcinoma appears to be increased in SOTR. Case reports exist for other types of rare skin cancer such as atypical fibroxanthoma, angiosarcoma, leiomyosarcoma, cutaneous T- and B cell lymphomas. However, these tumours are rare even in SOTR and no special recommendation is given.

Choice and modification of immunosuppressive regimen

Increased skin cancer in SOTR is mainly a result of the long-term immunosuppression that is needed to prevent graft rejection. Reduction of immunosuppression should thus be considered in all cases of recurrent or aggressive skin cancer, in particular SCC. The impact of reduced immunosuppression on the course of disease has not been well studied. Recent studies have therefore tried to find a consensus for recommended measures in SOTR affected by skin cancer [29]. The best evidence for reducing immunosuppression in post-transplant skin cancer exists for KS and can thus be recommended. A likely benefit for reduced immunosuppression exists in SCC and should thus be carefully evaluated by transplant physicians in moderate and severe cutaneous carcinogenesis, especially if more aggressive forms of SCC are present. For all other forms of skin cancer, reduction of immunosuppression may not outweigh the quality of life of maintaining immunosuppression (i.e., preventing rejection) and, thus, should be considered individually (recommendation D).

Several drugs within currently used immunosuppressive regimens are known to have cancer-promoting effects besides their immunosuppressive properties. Cyclosporine A (CsA) is known to increase levels of TGF β and VEGF which potentially can contribute to cutaneous carcinogenesis. The class of mTOR inhibitors on the other side has shown antiproliferative effects *in vitro* and *in vivo*. Several studies have shown that once mTOR inhibitors were either added to regimens with cal-

cineurin inhibitors or were substituted for calcineurin inhibitors, the rate of cutaneous malignancies decreased considerably [44]. These findings were not part of these studies' primary hypotheses, though, and there are currently multicentre trials in France, the Netherlands and Germany underway to validate the observation that mTOR inhibitors may decrease the incidence of SCC in SOTR. With results from these confirmatory trials pending, our current recommendation to transplant physicians is to consider a switch from calcineurin inhibitors to mTOR inhibitors in SOTR with stable transplant function in either (a) KS (recommendation C), or (b) moderate to severe cutaneous carcinogenesis of SCC (recommendation C).

Azathioprine has been shown to render cells susceptible to direct DNA damage by UVA, thus breaking a current paradigm that only UVB is absorbed by DNA with direct resulting damage in the form of cyclobutane pyrimidine dimers. Azathioprine may furthermore result in increased photosensitivity to UVA [45]. These two factors may explain why azathioprine is repeatedly incriminated in increased cutaneous carcinogenesis [46]. Our current recommendation to transplant physicians is to consider a switch from azathioprine to another antimetabolite such as mycophenolate mofetil in SOTR with stable transplant function with moderate to severe cutaneous carcinogenesis of SCC (recommendation D).

Systemic chemoprevention

Acitretin is a systemic retinoid that has proven beneficial in the prevention of SCC both in the general population and in the high-risk group of SOTR [47–49]. In the latter, the benefit may reach a dimension of 85% risk reduction for further SCC development. Our current recommendation to dermatologists is to consider the introduction of acitretin in SOTR with stable transplant function for moderate to severe cutaneous carcinogenesis of SCC, and earlier in selected cases (e.g., more aggressive forms of SCC, extensive field cancerisation, porokeratosis) (recommendation A). Acitretin is given long-term at a typical dose of 0.4 mg/kg body weight once daily p.o. (Neotigason®). Patient adherence is improved with a gradually increasing dosing schedule. We recommend initiation of acitretin at 10 mg in the morning every other day. After three weeks, dosage is increased to 10 mg daily for another 3 weeks. Dosage is then increased to 10 mg and 25 mg on alternating days for another 3 weeks. Eventually the typical maintenance dose of 25 mg daily is reached. Using such a strategy, every patient

will experience one dosing scheme of acitretin as well tolerable to which he may return should adverse effects develop at a higher dose later on (recommendation D). The most common, dose-dependent side effects are dryness of lips, mouth and skin in general and hair loss, but are rapidly reversible on dose reduction or cessation of acitretin. Liver transaminases should be monitored biweekly for the first two months and then quarterly for drug-induced hepatopathy. Triglycerides and cholesterol may increase and should be monitored quarterly. Combination with tetracyclines, methotrexate or vitamin A derivatives is contraindicated. Acitretin is known for its strong teratogenicity. Adequate contraception must be started before initiation and maintained for two years beyond a potential end of acitretin therapy.

Orally applied capecitabine, which converts to 5-fluorouracil systemically, has shown benefit in the chemoprevention for SOTRS in a small case series and may present an option in off-label use in the future [50].

Integrated care

The numbers of SOTR experiencing cutaneous adverse events in relation to transplantation, in particular skin cancer, are increasing. For optimal care of this frequently polymorbid population, a close collaboration between dermatologists and the transplant team is recommended both for patient education in prevention and for early treatment of evolving skin cancer. This should take place in secondary and tertiary medical centres where specialized organ transplant recipient clinics have been initiated within many dermatology departments. Here, a standard of care can be defined and maintained along with transplant physicians, medical residents can be trained focused on the special aspects of skin care in SOTR, and clinical as well as laboratory studies can be conducted. On the other hand, the increasing number of SOTR implies that all dermatologists should at some point be involved and educated in the particular needs of this patient group, because an increasing amount of care will also have to be provided in a peripheral setting outside the transplant centre. Exchange of individual clin-

ical information should thus not only take place between dermatologists and transplant physicians within large centres, but also between dermatologists at centres and those in the periphery. The main objectives of such an integrated care should be to recognize and communicate to all transplant physicians involved the current state of cutaneous carcinogenesis in a given SOTR. It is crucial that an occurrence of SCC is not seen as isolated event, but rather as one in a chain of events that may influence transplant decisions such as the choice of immunosuppressive regimen, treatments such as field cancerisation or systemic chemoprevention (recommendation D) and in some cases decisions regarding subsequent transplantations.

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